U.S. Multicenter Clinical Trial of Corneal Collagen Crosslinking for Treatment of Corneal Ectasia after Refractive Surgery

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Purpose: To evaluate the safety and efficacy of corneal collagen crosslinking (CXL) for the treatment of corneal ectasia after laser refractive surgery.

Design: Prospective, randomized, multicenter, controlled clinical trial.

Participants: One hundred seventy-nine subjects with corneal ectasia after previous refractive surgery.

Methods: The treatment group underwent standard CXL, and the sham control group received riboflavin alone without removal of the epithelium.

Main Outcome Measures: The primary efficacy criterion was the change over 1 year of topography-derived maximum keratometry (K), comparing treatment with control groups. Secondary outcomes evaluated were corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA), manifest refraction spherical equivalent, endothelial cell count, and adverse events.

Results: In the crosslinking treatment group, the maximum K value decreased by 0.7 diopters (D) from baseline to 1 year, whereas there was continued progression in the control group (1.3 D difference between treatment and control, $P < 0.0001$). In the treatment group, the maximum K value decreased by 2.0 D or more in 14 eyes (18%) and increased by 2.0 D or more in 3 eyes (4%). The CDVA improved by an average of 5.0 logarithm of the minimum angle of resolution (logMAR) letters. Twenty-three eyes (32%) gained and 3 eyes (4%) lost 10 or more logMAR letters. The UDVA improved 4.5 logMAR letters. Corneal haze was the most frequently reported crosslinking-related adverse finding.

Conclusions: Corneal collagen crosslinking was effective in improving the maximum K value, CDVA, and UDVA in eyes with corneal ectasia 1 year after treatment, with an excellent safety profile. CXL is the first approved procedure to diminish progression of this ectatic corneal process. *Ophthalmology 2017;124:1475-1484 © 2017 by the American Academy of Ophthalmology*

Corneal ectasia after laser refractive surgery is a keratoconus-like focal biomechanical disorder characterized by progressive distortion of the corneal shape and optical quality.[1] The pathogenesis of ectasia after laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK) remains unclear and may be multifactorial. In many cases, it is likely that the ectatic cornea harbored a predisposition to keratoconus preoperatively, with undiagnosed frank keratoconus, forme fruste keratoconus, or an otherwise clinically normal-appearing cornea.[2] In others, the possibility remains that removal of tissue during LASIK or PRK thins the corneal dome enough to destabilize its architectural structure, precipitating frank ectasia. Specific risk factors for ectasia include preoperative high myopia, thin residual stromal bed, total percentage of tissue altered, and most important, forme fruste keratoconus on preoperative topography.[3–5] Similar to keratoconus, there may be a loss or slippage of collagen fibrils and changes to the extracellular matrix in the ectatic corneal stroma.[6] Such changes are thought to cause biomechanical instability of the cornea with consequent changes in the cornea's anatomic and topographic architecture.[7] In post-LASIK ectasia, these changes are concentrated in the residual stromal bed.[8]

To date, there has been no treatment available to mitigate the progression of ectasia. As for keratoconus treatment, corneal collagen crosslinking (CXL) is thought to be beneficial in the setting of corneal ectasia by strengthening and stabilizing the corneal architectural structure. By biomechanically stiffening the cornea, the clinical goal of CXL is to decrease disease progression, thus preventing further loss of vision.

We report the results of CXL for the treatment of corneal ectasia in 179 subjects enrolled in the U.S. Phase III, multicenter, prospective, randomized, sham-controlled, clinical trials of crosslinking over a 1-year postoperative period. On the basis of these safety and efficacy outcomes, CXL for the treatment of corneal ectasia after refractive surgery was approved by the U.S. Food and Drug Administration (FDA) in July 2016.

Methods

Patients were enrolled as part of 2 multicenter prospective, randomized, sham-controlled clinical trials: CXL with Photrexa

Table 1. Preoperative Population Characteristics

	CXL Group	Control Group	Total
N	91	88	179
Age (yrs)	43.5	41.8	42.7
Gender (F/M)	33/58 (36/64%)	24/64 (27/73%)	57/122 (32/68%)
Mean maximum K (SD)	55.4 D (±6.86 SD)	54.8 D (±6.40 SD)	55.1 D
Preceding refractive surgery			
LASIK only	83 (91%)	83 (94%)	166 (93%)
LASIK and PRK	4 (4%)	4 (5%)	8 (5%)
PRK only	4 (4%)	1 (1%)	5 (3%)

CXL = corneal collagen crosslinking; D = diopters; K = keratometry; PRK = photorefractive keratectomy; SD = standard deviation.

Viscous (0.1% riboflavin ophthalmic solution/20% dextran), Photrexa (0.1% riboflavin ophthalmic solution), and the KXL System (Avedro Inc., Waltham MA) to treat corneal ectasia after refractive surgery. The studies were performed under the guidelines of the U.S. FDA (New Drug Application no. 203324) and approved and monitored by an investigational review board (clinicatrials.gov; no. NCT00674661). The studies were compliant with the U.S. Health Insurance Portability and Accountability Act. All patients provided informed consent. Randomization was computer generated, and on the procedure day, a sealed envelope was opened by the investigator to reveal whether the eye would be in the control or treatment group. Both patients and investigators were aware of the randomly assigned group.

Inclusion criteria included patients 14 years of age or older, axial topography pattern consistent with corneal ectasia (including relative inferior steepening with inferior:superior difference ≥1.5 diopters [D]), corrected distance visual acuity [CDVA] worse than 20/20, and corneal thickness as measured on Pentacam (Oculus GmbH, Wetzlar, Germany) of ≥300 μm at the thinnest area. Exclusion criteria included patients with a history of corneal surgery other than laser refractive surgery, including intracorneal ring segments, corneal pachymetry less than 300 μm, and a history of corneal disease that would interfere with healing after the procedure, such as chemical injury or delayed epithelial healing in the past. Patients pregnant or lactating during the course of the study were excluded.

Crosslinking and Sham Control Treatments

Contact lens wearers were instructed to discontinue spherical soft lenses for a minimum of 3 days and soft toric and rigid-gas permeable lenses for a minimum of 2 weeks before the preoperative eye examination. Thereafter, they were required to show a stable refraction at 2 examinations that were at least 7 days apart. Stability was determined by comparing manifest refraction spherical equivalent (MRSE) and maximum keratometry (K) measurements between the 2 visits and ascertaining that they did not differ by more than 0.75 D.

Patients were initially randomized into a treatment or sham control group. The treatment group received standard ultraviolet A (UVA)−riboflavin 0.1% CXL treatment, performed according to the methodology described by Wollensak et al.[9] Initially, a topical anesthetic agent was administered and the central 9.0-mm epithelium was removed by mechanical debridement with a blunt spatula. Riboflavin (0.1% in 20% dextran T500 solution) was then administered topically every 2 minutes for 30 minutes. Riboflavin absorption throughout the corneal stroma and anterior chamber flare was confirmed by slit-lamp examination.

Ultrasound pachymetry was performed, and if the cornea was thinner than 400 μm at any point within the treatment area, hypotonic riboflavin (0.1% riboflavin, no dextran) was administered, 1 drop every 10 seconds for 2-minute sessions, after which ultrasound pachymetry was performed to ascertain that the stroma had swollen to more than 400 μm. This was repeated in 2-minute sessions until adequate corneal thickness was obtained. The cornea was aligned and exposed to UVA 365 nm light for 30 minutes at an irradiance of 3.0 mW/cm^2 (UV-X system, IROC AG, Zurich, Switzerland).

During UVA exposure, administration of the riboflavin/dextran solution was continued every 2 minutes. Postoperatively, antibiotic and corticosteroid drops were administered, a soft contact lens bandage was placed, and the eye was reexamined at the slit-lamp. The contact lens was removed after the epithelial defect had closed. Antibiotics and corticosteroid (prednisolone acetate 1%) drops were continued 4 times daily for 1 week and 2 weeks, respectively. Patients were followed for 12 months postoperatively and had complete examinations at 1, 3, 6, and 12 months in predetermined windows.

The sham control group received riboflavin 0.1%/dextran ophthalmic solution alone. In this group, the epithelium was not removed. Riboflavin was administered topically every 2 minutes for 30 minutes. Next, the cornea was exposed to a sham treatment in which the UVA light was not turned on, during which time

Table 2. Postoperative Topographic Maximum Keratometry after Crosslinking

Group	Preoperative (n)	Postoperative Mean Maximum K (D) ± SD				12-Month CXL vs. Control (Maximum K Change)
		1 Month (n)	3 Months (n)	6 Months (n)	12 Months (n)	
CXL	55.4±6.9 (91)	56.2±7.2 (88)	55.5±7.0 (88)	54.7±6.5 (84)	54.7±6.9 (76)	P < 0.0001*
CXL (LOCF)	55.4±6.9 (91)	56.4±7.2 (91)	55.3±7.0 (91)	54.9±6.6 (91)	54.7±6.8† (91)	
Control	54.8±6.4 (88)	55.0±6.5 (86)	55.1±6.4 (85)	54.6±6.1 (32)	56.9±3.5 (2)	
Control (LOCF)	54.8±6.4 (88)	55.0±6.5 (88)	55.5±6.7 (88)	55.4±6.7 (88)	55.4±6.7† (88)	

CXL = corneal collagen crosslinking; D = diopters; K = keratometry; LOCF = last observation carried forward; SD = standard deviation.
*Significant difference between treatment and control groups (LOCF analysis). P value is on difference between CXL and control (2-sided t test; significance level 0.05).
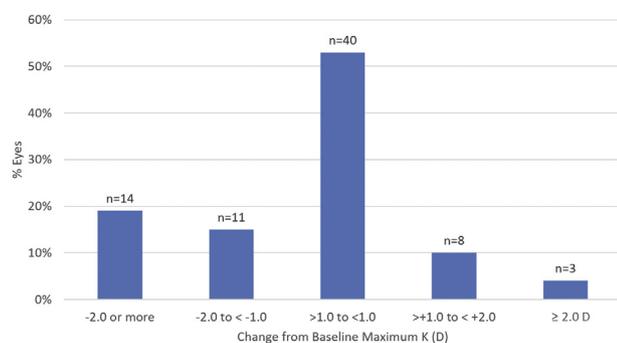†Significant difference within group between preoperative and 1-year postoperative values.

Figure 1. Change in maximum K in individual eyes between baseline and 12 months after crosslinking. D = diopters; K = keratometry.

Figure 2. Change in maximum K over time. K = keratometry.

riboflavin was administered topically every 2 minutes for an additional 30 minutes. The sham control patients had complete examinations at 1 and 3 months in predetermined windows. Per the study protocol, the patient was allowed to cross over and receive full CXL treatment after the 3-month follow-up examination. Because all such patients had met the inclusion criteria for the study and anticipated ultimate treatment, the actual decision to cross over to treatment after the 3-month evaluation was made jointly by patient and physician at that time. In patients who met the study criteria in their fellow eye, the decision to proceed with fellow eye treatment was made after the 3-month follow-up window.

Outcome Measures

Topography. Topography measurements were obtained using a rotating Scheimpflug camera (Pentacam HR, Oculus GmBH). Topographic data were obtained preoperatively and 1, 3, 6, and 12 months postoperatively. For quantification of corneal curvature, maximum K on the Scheimpflug system was analyzed. Maximum K was chosen as the primary efficacy outcome because it measures a salient feature of corneal ectasia, that is, the steepness of the ectatic topographic distortion. Moreover, topographic maximum K afforded an objective, quantitative end point and allowed consistent hardware and software among the study sites. A difference of at least 1.0 D in the mean change in maximum K from baseline to the 1-year follow-up comparing the treatment and control group was selected as a clinically meaningful outcome to define study success; that is, topographic flattening in the treatment group or relative steepening in the control group indicated procedure efficacy.

Visual Acuity and Refraction. The uncorrected distance visual acuity (UDVA), CDVA, and manifest subjective refraction were measured preoperatively and postoperatively at 1, 3, 6, and 12 months. Visual acuity measurements were obtained under controlled lighting conditions using a modified Lighthouse Early Treatment of Diabetic Retinopathy Study visual acuity chart (2nd edition) with Sloan letters. Patients were tested 4 m from the visual acuity chart. If patients could not read any letters at 4 m, they were tested at 2 m. Visual acuity was recorded and analyzed as the number of Early Treatment Diabetic Retinopathy Study logarithm of the minimum angle of resolution letters read.[10]

Patient Questionnaire. All patients were asked to fill out a questionnaire, which scored various subjective vision function parameters. Outcomes of subjectively noted photophobia, difficulty in night driving, difficulty in reading, diplopia, fluctuations in vision, glare, halo, starburst, dryness, pain, and foreign body sensation were assessed. The parameters were scored on a scale of 1 (none), 2 (mild), 3 (moderate), 4 (marked), and 5 (severe). The questionnaire was filled out preoperatively and again at 1 year
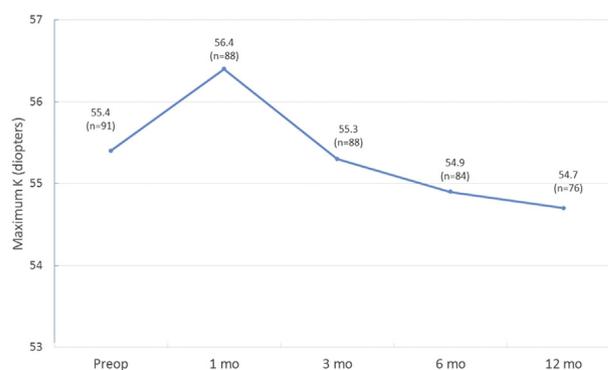
postoperatively. The data are presented as the mean subjective visual score for each of the 11 parameters queried.

Safety Analysis

A total of 219 eyes comprised the safety database and included eyes initially treated with crosslinking, eyes in the control group that crossed over to treatment, and fellow eyes that underwent crosslinking. Any adverse events were noted at each study visit and at any unscheduled visit. Endothelial cell count was obtained using specular microscopy (Konan Medical Inc., Irvine, CA) preoperatively and at 12 months, postoperatively. Three measurements were taken, and the average cell count for each eye was used in the analysis. A consistent cohort of each treatment group was used to analyze changes over time.

Statistical Analysis

The study presented in this article incorporates the pooled data of 2 individual clinical trials, accomplished among 11 study sites. Both trials were run concurrently, had identical inclusion and exclusion criteria, and followed the identical procedural and follow-up protocol.

All safety and efficacy analyses were completed using the intent-to-treat population. All analyses are presented by treatment group. The intent-to-treat population consisted of all treated subjects analyzed according to randomized treatment. Randomization was generated by the sponsor and allocated to each study site in a numbered sequence of envelopes containing subject assignment. The randomization envelope was opened by the individual investigator just before patient treatment.

All efficacy analyses were performed by visit, and although *P* values are reported, the only ones that were used for statistical inference are the final analysis of month 12 data (alpha <0.05, 2-sided *t* test). The baseline score for all end points was defined as the preoperative measurement closest to the treatment date. For all efficacy analyses, only the randomized eyes were included, that is, efficacy analyses comprised 179 eyes of 179 patients and did not include crossover or fellow eye outcomes.

The primary efficacy end point was the difference between the CXL group and the control group for the mean change in maximum K from baseline to month 12, with a ≥1.0 D difference between treatment and control hypothesized as a clinically significant difference. The primary end point data were summarized using descriptive statistics, and the differences in mean changes between the CXL treatment group and the control group at each time point were evaluated using a 2-sample *t* test to test the following hypothesis:

$$H_0 : \mu CXL - \mu C = 0 \text{ versus } H_A : \mu CXL - \mu C \neq 0$$

where H_0 is the null hypothesis and H_a is the statistical hypotheses for the primary efficacy end point, μC is the mean difference

Table 3. Postoperative Visual Acuity after Crosslinking

| Group | Preoperative (n) | Mean ETDRS logMAR Letters ± SD | | | | 12-Month CXL vs. Control (CDVA) |
		1 Month (n)	3 Months (n)	6 Months (n)	12 Months (n)	
CDVA						
CXL	37.0±13.0 (91)	35.2±13.7 (89)	39.9±12.8 (87)	41.3±14.1 (83)	41.2±13.7 (75)	<0.0001*
CXL (LOCF)	37.0±13.0 (91)	35.4±13.6 (91)	40.1±12.6 (91)	41.0±13.7 (91)	42.0±12.9[†] (91)	
Control	38.1±12.4 (88)	38.6±12.5 (86)	38.8±12.6 (82)	37.5±13.2 (31)	41.0±5.7 (2)	
Control (LOCF)	38.1±12.4 (88)	38.6±12.4 (88)	38.5±12.6 (88)	37.7±12.5 (88)	37.8±12.6 (88)	
UDVA						
CXL	14.4±13.5 (91)	16.0±14.1 (89)	16.9±14.9 (86)	18.9±15.7 (82)	19.0±16.2 (75)	<0.001*
CXL (LOCF)	14.4±13.5 (91)	15.7±14.1 (91)	17.3±15.2 (91)	18.7±15.5 (91)	18.9±16.0[†] (91)	
Control	15.0±13.6 (88)	16.3±13.3 (87)	15.8±13.0 (83)	13.7±12.9 (32)	11.0±8.5 (2)	
Control (LOCF)	15.0±13.6 (88)	16.2±13.2 (88)	16.0±13.1 (88)	14.9±12.9 (88)	14.9±12.9 (88)	

CDVA = corrected distance visual acuity; CXL = corneal collagen crosslinking; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = last observation carried forward; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation; UDVA = uncorrected distance visual acuity.
*Significant difference between treatment and control groups (LOCF analysis). P value is on difference between CXL and control (2-sided t test; significance level 0.05).
[†]Significant difference within group between preoperative and 1-year postoperative values.

between the post-baseline maximum K and the baseline maximum K for the control group, and μCXL is the mean difference between the post-baseline maximum K and the baseline maximum K for the CXL group. A *P* value ≤ 0.05 was considered statistically significant.

A last observation carried forward (LOCF) method was used to impute missing data for the 12-month analysis. Because the control group was eligible to receive treatment after the month 3 visit, those eyes that then received treatment were lost to follow-up. Therefore, in the LOCF analysis, efficacy data before crossover were carried forward to month 12, the study end point.

For all reported adverse events, the number of distinct treatment-emergent events and the number and percent of subjects who experienced the event were summarized by group and categorized by system organ class and preferred term using the Medical Dictionary for Drug Regulatory Affairs 14.1. The data are presented with events listed by preferred term in order of decreasing frequency in the treatment group. No formal statistical analysis was conducted on the adverse event data.

Results

Subject Baseline Demographics and Disposition

A total of 91 eyes were treated in the CXL treatment group, and 88 eyes were treated in the sham control group. Of these, 78 eyes (85.7%) and 72 eyes (81.8%), respectively, remained in the study through the 12-month follow-up. A total of 166 eyes had undergone previous LASIK, 8 eyes had undergone initial LASIK with PRK retreatment, and 5 eyes had undergone PRK. Subject demographics are presented in Table 1.

Postoperative Topography Changes after Corneal Collagen Crosslinking

Maximum Keratometry. In the CXL treatment group, there was a significant decrease in the mean maximum K value (0.7±2.1 D) between preoperatively and 12 months postoperatively (*P* < 0.05) (Table 2). In the control group, there was a significant increase in
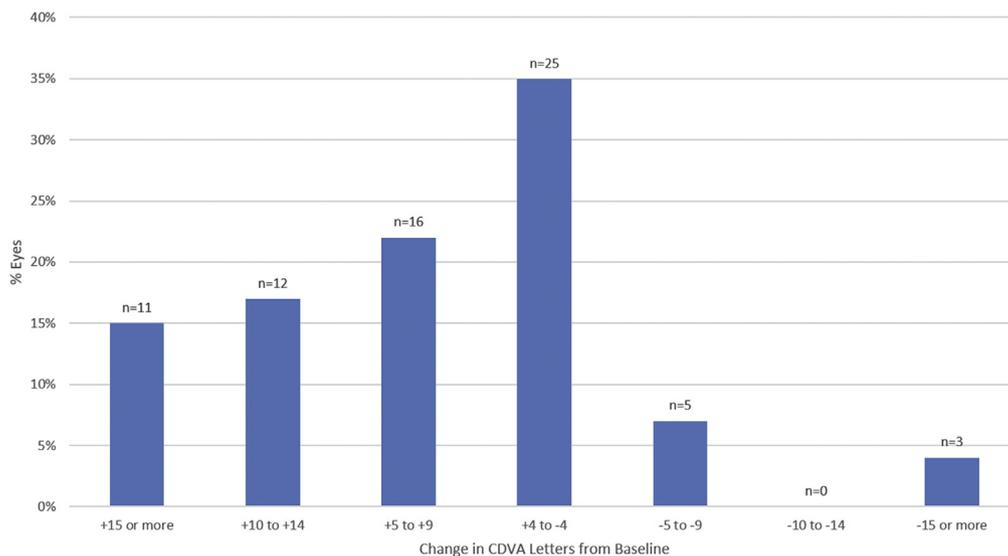

Figure 3. Change in corrected distance visual acuity (CDVA) (letters read) in individual eyes between baseline and 12 months after crosslinking.
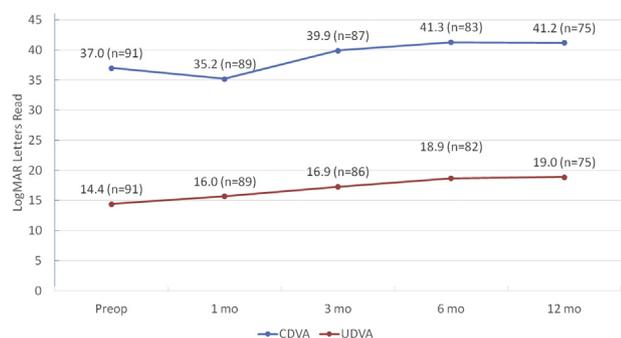
Figure 4. Change in CDVA and uncorrected visual acuity (UCVA) over time. CDVA = corrected distance visual acuity; logMAR = logarithm of the minimum angle of resolution.

the mean maximum K value (0.6±2.1 D) between preoperatively and 12 months postoperatively ($P < 0.05$). The difference between maximum K change between treatment and control was 1.3 D, a statistically significant finding ($P < 0.0001$).

In eyes with 12 months follow-up maximum K data (n = 76), the maximum K decreased by 2.00 D or more in 14 eyes (18%), remained within 2 D in 59 eyes (78%), and increased by 2.00 D or more in 3 eyes (4%) (Fig 1). With regard to the time course of outcomes evolution in the crosslinking treatment group, mean maximum K increased by 1.0 D at month 1, decreased by 1.1 D between months 1 and 3, and continued to decrease by 0.4 D between months 3 and 6 and 0.2 D between months 6 and 12 (Fig 2).

Visual Acuity

Corrected Distance. Table 3 shows the CDVA at each follow-up examination. In the crosslinking treatment group, there was a significant improvement of 5.0 letters of visual acuity between preoperatively and 12 months postoperatively. In the control group, there was a loss of 0.3 letters. The difference in CDVA change at 1 year between CXL treatment and control was 5.3 letters, a statistically significant finding ($P < 0.0001$).

In eyes with 12 months follow-up CDVA data (n = 72), the CDVA improved by 10 or more letters in 23 eyes (32%), improved by 1 to 9 letters in 32 eyes (44%), remained unchanged or decreased 0 to 9 letters in 14 eyes (19%), and decreased 10 letters or more in 3 eyes (4%) (Fig 3). Of the 3 eyes losing 10 or more letters, there was no obvious clinical correlate. All 3 showed stable topography, with no change in maximum K from baseline to 12 months. One eye was reported to have Vogt's striae; there were no other adverse events reported in these eyes.

Over the time course of the study, mean CDVA decreased by 1.8 letters at month 1 and increased by 4.7 letters between months 1 and 3, with further improvement of 0.4 letters between months 3 and 6, and a decrease of 0.1 letter between months 6 and 12 (Fig 4).

Uncorrected Distance. Table 3 shows the UDVA at each follow-up examinations. In the crosslinking treatment group, there was a significant improvement of 4.5 letters of visual acuity between preoperatively and 12 months postoperatively. In the control group, there was a loss of 0.1 letter. The difference in UDVA change at 1 year between CXL treatment and control was 4.6 letters, a statistically significant finding ($P < 0.001$).

Over the time course of the study, mean UDVA increased by 1.6 letters at month 1, 0.9 letter between months 1 and 3, with further improvement of 2.0 letters between months 3 and 6, and 0.1 letter between months 6 and 12 (Fig 4).

Refractive Changes

Table 4 shows the MRSE at each follow-up visit. In the CXL treatment group, there was a 0.5 D decrease in MRSE myopia between preoperatively and 12 months postoperatively. In the control group, there was a decrease of 0.1 D. The difference in MRSE change at 1 year between CXL treatment and control was not statistically significant.

Subjective Patient Questionnaire

Ten of 11 parameters analyzed in the study showed improvement after 12 months in the CXL treatment group. Only "difficulty driving at night" was statistically significant. Figure 5 details the results of all preoperative and postoperative symptoms analyzed.

Adverse Events

Table 5 lists all adverse events that were reported at a rate of >5% comparing treatment and control through the 3-month follow-up examination. Most of these were related to epithelial debridement at surgery and subsequent re-epithelialization. There was 1 severe ocular adverse event reported. A 47-year-old patient in the crosslinking treatment group was reported to have epithelial ingrowth beneath the LASIK flap on postoperative day 35. The LASIK flap was lifted, and the ingrown cells were removed with resolution of the adverse event. At the final 12-month visit, there were 6 eyes with reported adverse events: persistent corneal haze in 5 eyes and corneal scar in 1 eye.

Corneal Haze

Corneal stromal haze or demarcation line was noted in 62 eyes (68%) at any examination throughout this study. At the 12-month follow-up, 5 eyes remained with stromal haze and 1 eye remained with corneal scar. The first patient with residual haze showed improvement of 1 D in maximum K, 14-letter improvement in uncorrected visual acuity (UCVA), and 9-letter improvement in CDVA. The second patient showed steepening of 1 D, 3-letter improvement in UCVA, and 30-letter improvement in CDVA. The third patient showed improvement of 4 D in maximum K, 3-letter improvement in UCVA, and 4-letter improvement in CDVA. The fourth patient showed improvement of 3 D in

Table 4. Postoperative Manifest Refraction Spherical Equivalent after Crosslinking

		Mean MRSE (D)			
	Preoperatively (n)	*1 Month (n)*	*3 Months (n)*	*6 Months (n)*	*12 Months (n)*
CXL	−3.1±4.1 (91)	−2.9±4.1 (89)	−3.0±3.7 (88)	−3.0±3.8 (84)	−2.4±4.1 (76)
CXL (LOCF)	−3.1±4.1 (91)	−3.1±4.2 (91)	−2.9±3.6 (91)	−2.9±3.7 (91)	−2.6±4.0 (91)
Control	−3.7±4.4 (88)	−3.5±4.5 (101)	−3.7±4.6 (84)	−4.4±5.5 (32)	−5.4±3.6 (2)
Control (LOCF)	−3.7±4.4 (88)	−3.5±4.5 (88)	−3.6±4.5 (88)	−3.6±4.6 (88)	−3.6±4.6 (88)

CXL = corneal collagen crosslinking; D = diopters; LOCF = last observation carried forward; MRSE = manifest refraction spherical equivalent.
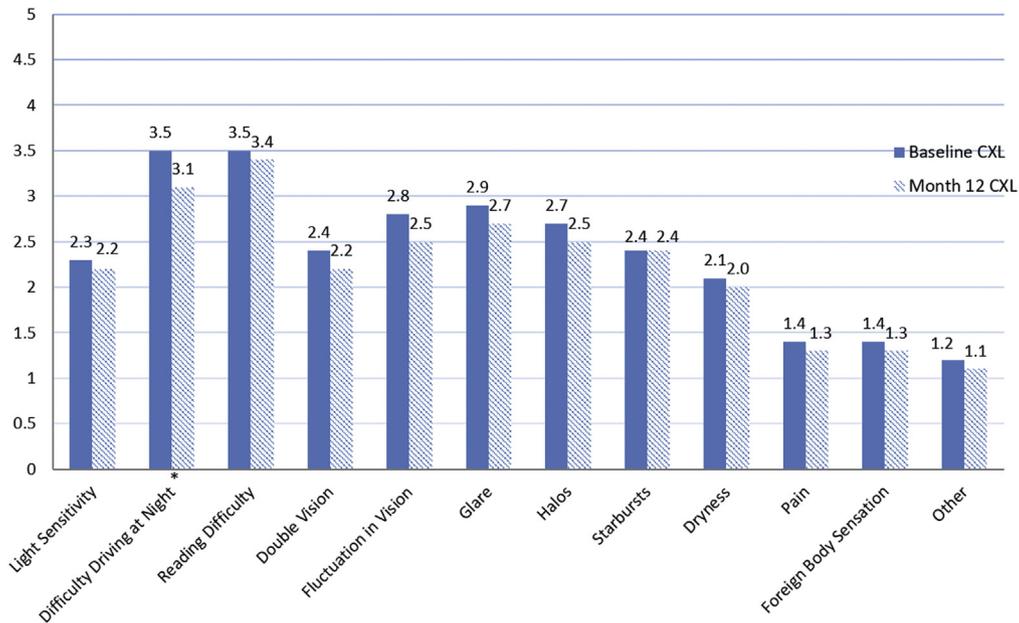
Figure 5. Mean rating of subjective visual parameters preoperatively and 12 months after crosslinking (scale = 1−5; *statistical significance $P < 0.05$). CXL = corneal collagen crosslinking.

maximum K, no change in UCVA, and 5-letter improvement in CDVA. The last patient with residual haze showed 1 D worsening of maximum K, no change in UCVA, and 5-letter worsening of CDVA. In the patient with reported corneal scar, maximum K worsened by 1 D, UCVA improved 6 letters, and CDVA remained unchanged.

Endothelial Cell Analysis

Table 6 presents endothelial cell density (ECD) analyses comparing the crosslinking treatment group with the control group at 3 months and within the treatment group at 12 months. There was no statistically significant difference in cell count change between the 2 groups. Over the course of 1 year, the treatment group had an average decrease in ECD of 4.5%. Figure 6 shows the 1-year change in ECD stratified to individual mean gain or loss of cells. There were no reported cases of persistent corneal edema in the study.

Discussion

This article presents the outcomes of the U.S. multicenter, randomized, controlled clinical trial of corneal crosslinking for the treatment of corneal ectasia after laser refractive surgery. Ectasia after LASIK was first reported in 1998.[1,11] Like keratoconus, ectasia is a progressive process typified by increasing distortion of the cornea's optical architecture leading to loss of visual function.[12]

Heretofore, there has been no modality available to stabilize the ectatic cornea and decrease disease progression. Thus, the development of CXL has been of great anticipation to clinicians and patients alike. In this study, maximum K of the ectatic cornea decreased by 0.7 D over 1 year after treatment, compared with continued progression in the control group, suggesting that CXL would be beneficial in improving the disease prognosis. Therefore, the recent FDA

approval of CXL for both the indications of progressive keratoconus and ectasia after refractive surgery represents a major advance in clinical care. Indeed, a recent study from investigators in Norway reported a substantial decrease in the frequency of keratoplasty in patients with keratoconus after the widespread introduction of crosslinking in the country.[13]

By means of riboflavin-ultraviolet (UV)−militated corneal crosslinking and consequent biomechanical strengthening, the essential clinical goal of CXL in ectasia, as in keratoconus, is to decrease disease progression over time. Given this goal, we used maximum K as a proxy for ectasia severity; thus, changes in maximum K were used as an indicator of improvement, stability, or progression of the ectatic condition. A difference of at least 1.0 D in the mean

Table 5. Ocular Adverse Events in >5% of Subjects after Crosslinking*

	CXL Treatment Group (n = 91) (%)	Control Group (n = 88) (%)
Corneal opacity (haze)	68	8
Punctate keratitis	20	3
Corneal striae	9	7
Epithelial defect after 1 wk	26	3
Eye pain	26	0
Blurred vision	17	5
Photophobia	19	0
Dry eye	14	5
Decreased visual acuity	11	1
Increased lacrimation	10	1
Ocular irritation	9	1

CXL = corneal collagen crosslinking.
*Any examination after treatment through 3 months of follow-up.

Table 6. Endothelial Cell Density*

	Baseline ECD	3-Month ECD	Change Baseline to 3 Months	12-Month ECD	Change Baseline to 12 Months
CXL treatment (n = 62)	2469±437	2418±340	−51 (−2.1%)	2357±364	−113 (−4.5%)
Control (n = 71)	2594±431	2541±395	−53 (−2.0%)	NA	NA

CXL = corneal collagen crosslinking; ECD = endothelial cell density; NA = not available.
*Consistent cohort.

change in maximum K from baseline to 1 year, comparing the treatment and control group, was chosen as the primary outcome indicator of success in improving disease prognosis. It should be noted that although the UV-X system was used as the UV light source in this study, FDA approval was, specifically, for crosslinking using the commercially produced KXL System (Avedro Inc., Waltham, MA). Technical documentation submitted to the FDA shows that there is no notable difference in UV wavelength or energy delivered, or other attributes of the actual UV light between the systems.

Topography Changes after Crosslinking

The mean maximum K value of the crosslinking treatment group decreased by 0.7 D at 1 year compared with 0.6 D steepening of the control group, a difference of 1.3 D between treatment and control. Thus, crosslinking does appear, generally, to have a beneficial effect on corneal topography in ectasia patients over 1 year. When clinically evaluating these average responses, it is elucidating, and may aid the ophthalmologist in counseling appropriate patient expectations, to consider results as proportions of patients with good and bad outcomes. Thus, the maximum K value decreased by 2.0 D or more in 14 eyes (18%), a clinically significant improvement in corneal topography, whereas it increased by 2.0 D or more in 3 eyes (4%) (Fig 1). Although these latter 3 eyes might be considered treatment failures because disease progression was not

stabilized,[14] it is unclear if CXL in these cases was ineffective or simply did not slow progression completely.

Given this variation in individual patient outcomes, proper patient selection for crosslinking will be an important consideration for clinicians as they implement this new treatment. With regard to this, in an effort to define preoperative characteristics that might influence outcomes, a previously published multifactorial analysis from one author (PSH) of a single-center cohort from this study suggests that eyes with preoperatively steeper corneas have a greater likelihood of topography improvement 1 year postoperatively.[15] Controlling for preoperative factors, including gender, age, maximum K, UDVA, CDVA, and corneal thickness, the only independent predictor of topography improvement was preoperative maximum K; eyes with a maximum K of 55.0 D or more were found to be 5.4 times more likely to have topographic flattening of 2.0 D or more, compared with eyes with flatter corneas. Looking specifically at factors associated with failure of crosslinking to stabilize the cornea, even to a more refined 1.0 D threshold, there were no independent predictors.

Vision Changes after Crosslinking

In addition to the primary efficacy measurement of maximum K, an improvement in CDVA may indicate another clinical advantage of CXL; conversely, any loss of CDVA is particularly important with regard to procedure
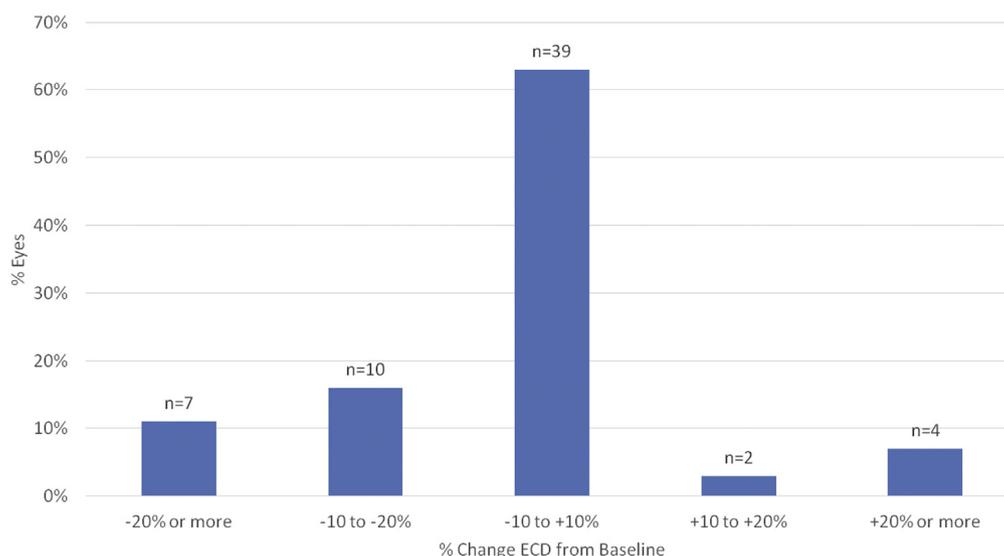

Figure 6. Change in endothelial cell count between baseline and 12 months after crosslinking. ECD = endothelial cell density.

safety. Because decrease in vision in ectasia results from distorted corneal optics, the improvement in maximum K that we found would be expected to yield improved visual function. Corroborating and expanding beyond this topographic outcome measure, previous studies of corneal topography indices[16] and wavefront-derived higher order aberrations[17] by one of the authors (PSH) showed a general improvement in both after crosslinking.

Indeed, crosslinking was associated with improvement of approximately 1 line of mean CDVA at 1 year postoperatively. Although this finding was statistically significant, the actual clinical significance is better illustrated by studying the outcomes on an individual basis; among patients receiving CXL, 23 eyes (32%) gained 2 or more lines of CDVA, whereas 3 eyes (4%) lost 2 lines or more (Fig 3). Thus, approximately one third of patients had a clinically meaningful increase in CDVA as a result of crosslinking, whereas a small number of eyes did continue to worsen.

In the aforementioned multifactorial analysis,[15] the only independent predictor of a change in postoperative CDVA after CXL was the preoperative CDVA; those eyes with worse preoperative CDVA ($\leq 20/40$) were $5.9\times$ more likely to experience an improvement in vision 1 year after crosslinking than eyes with 20/40 or worse preoperative CDVA. However, with regard to eyes that lost vision from the procedure, the most salient indicator of an unwanted outcome, there were no preoperative predictors.

Clinical Time Course after Crosslinking

As found for keratoconus, topography and vision outcomes seem to follow a reproducible time course, with an increase in maximum K at 1 month, thereafter followed by improvement[18] (Fig 2). The time course of CDVA change was similar, with a slight decrease at 1 month followed by improvement (Fig 4). An understanding of this natural tempo of outcomes evolution after crosslinking is important to properly guide postoperative follow-up and patient expectations. As discussed in our article on crosslinking for keratoconus,[19] this clinical time course likely is related to both epithelial and stromal wound healing and remodeling occurring over a year's timeframe.[20–24] Concomitant with these structural and physiologic responses, the appearance and resolution of corneal haze after CXL (discussed next) mirror this clinical response curve.[25]

Safety of Corneal Crosslinking

As for keratoconus, CXL for ectasia seems to have an excellent safety profile. Corneal stromal haze and the appearance of a demarcation line, apparently a normal and predictable response to CXL, were the most frequently reported adverse events in the study.[25,26] As shown in a previously published study from one author (P.S.H.), concurrent with both the clinical time course and the structural and physiologic responses outlined earlier, corneal haze maximizes at 1 month, plateaus at 3 months, and then improves to baseline over the next 9 months.[27] As we have stressed in previous reports, it is unclear whether postoperative haze is an unwanted complication or,

actually, a clinical sign of adequate crosslinking and a clinically beneficial wound-healing effect.

As in our multicenter study of keratoconus,[19] the ectasia eyes showed no damage to the corneal endothelium, and there were no reports of corneal decompensation after crosslinking. Per the study protocol, corneas needed to be swollen with a hypotonic riboflavin solution to a 400 μ threshold before proceeding with UV exposure to attenuate the UV power and protect the endothelium.[28,29] Other studies have confirmed that current crosslinking techniques generally are safe for the endothelium.[30,31] However, although there were no cases of corneal decompensation in our study, there have been cases of corneal edema reported after CXL.[32]

Most adverse events were related to removal of the epithelium during the crosslinking procedure. Indeed, the one reported severe adverse event was a case of epithelial ingrowth under the LASIK flap, likely militated by epithelial removal and possible flap edge trauma. Thus, the surgeon should take care not to damage the LASIK flap during epithelial debridement; avoidance of the flap edge might be appropriate.

Study Limitations

Our study is limited by 2 attributes of the control group. First, eyes in the control group were allowed to cross over to treatment at 3 months. Thus, most crossover eyes were lost to follow-up with regard to further control data; only 2 control eyes were available at 12 months. Because of this loss of data from crossover eyes, an LOCF analysis was used to impute missing data for 12-month analysis of treatment versus control; in these analyses, data before crossover was carried forward to follow-up windows in which actual data could no longer be obtained. Given the typical course of untreated ectasia, using an LOCF model to compare treatment and control would be expected to be a conservative methodology to compare the efficacy of CXL treatment with control; LOCF should bias the study toward a negative outcome because the data would be imputed going forward as no change, whereas disease progression, generally, would be expected in the setting of corneal ectasia. A second limitation of the control group is that the epithelium was not removed in these eyes. Therefore, any contribution of de-epithelialization, rather than the UVA light treatment, to patient outcomes was not accounted for by this control group methodology. Finally, with regard to outcomes of CXL comparing ectasia after LASIK with ectasia after PRK, we are unable to draw conclusions; only 4 eyes in the study had ectasia after PRK. The average preoperative maximum K in these 4 eyes was 60.0 ± 11.0 D and decreased to 59.8 ± 9.2 D at 1 year.

In conclusion, this randomized, controlled clinical trial demonstrates the efficacy and safety of CXL for the treatment of corneal ectasia. As demonstrated for keratoconus treatment, crosslinking, in addition to decreasing disease progression, also can have beneficial visual and optical effects such as decrease in corneal steepness and improvement in visual acuity in some patients. Certainly, the topography and visual results reported support the efficacy of crosslinking for the stabilization of the cornea in the setting of corneal ectasia after laser refractive surgery.

Appendix 1. U.S. Crosslinking Study Group

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Footnotes and Financial Disclosures

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Overall responsibility: Hersh

Abbreviations and Acronyms:

CDVA = corrected distance visual acuity; **CXL** = corneal collagen crosslinking; **D** = diopters; **ECD** = endothelial cell density; **FDA** = Food and Drug Administration; **K** = keratometry; **LOCF** = last observation carried forward; **logMAR** = logarithm of the minimum angle of resolution; **MRSE** = manifest refraction spherical equivalent; **PRK** = photorefractive keratectomy; **UCVA** = uncorrected visual acuity; **UDVA** = uncorrected distance visual acuity; **UV** = ultraviolet; **UVA** = ultraviolet A.

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